REMARKS

On page 2 of the Office Action, the Examiner issues a restriction requirement to one of the inventions of the following groups:

Group I - Claims 13-19, drawn to an immunogenic *Actinobacillus pleoropneumoniae* APP strain and a vaccine composition;

Group II - Claims 20-21, drawn to an *Actinobacillus pleoropneumoniae* CECT 5985 strain and a vaccine composition;

Group III - Claims 22-23, drawn to an *Actinobacillus pleoropneumoniae* CECT 5994 strain and a vaccine composition; or

Group IV - Claims 24-29, drawn to method of obtaining an immunogenic *Actinobacillus pleoropneumoniae* APP strain and a vaccine composition.

The Examiner contends that restriction is proper because the inventions do not relate to a single general inventive concept that has a common technical feature patentable over the prior art, i.e., the Examiner contends that Reimer et al teaches genes of apxIA and apxIIA of *Actinobacillus pleoropneumoniae*.

Applicants hereby elect the invention of Group I, with traverse. The Examiner is requested to note that the common technical feature patentable over the prior art is not the noted genes, but a mutation in the noted genes, especially a mutation in the transmembrane domain of ApxI, and optionally also, in the

transmembrane domain of ApxII, such that the strain is immunogenic and non-haemolytic. Thus, the claims are directed to mutated genes, not the wild-type genes.

Reimer et al does not teach or suggest such mutations nor production of immunogenic and non-haemolytic strains containing said mutations. Specifically, Reimer et al refers to research carried out at molecular level of the role of exotoxins ApxI and ApxII in the virulence of *Actinobacillus pleuropneumoniae* serotype 5.

In Reimer et al, four strains of *Actinobacillus pleuropneumoniae* are described, as can be seen in the first group described in Table 1 (at page 202 thereof):

Table 1 Bacterial strains and plasmids used in this study

Strain or plasmid	Characteristics	Source or Reference
A. *pleuropneumoniae*		
J45	Field isolate, ApxI$^+$, ApxII$^+$	33
mIT4-H	Chemical mutant, *apxICABD*$^-$, ApxI$^-$, ApxII$^-$	12
mIT4-H/pJFF801	mIT4-H containing pJFF801, ApxI$^-$, ApxII$^+$, Cm^r	This work
mIT4-H/pJFF800	mIT4-H containing pJFF800, ApxI$^+$, ApxII$^+$; Cm^r	This work
E. coli		
JF850	strain K12 XL1-Blue, *endA1, hsdR17* (rk−, mk+), *supE44, thi-1, RecA1, gyrA96, re1A1, Δlac* [F′, *proAB, lacL*^{q}, *lacZ*ΔM15, Tn10(tet^r)], pJFF800, *apxICABD*$^+$, Cm^r	This work
Plasmids		
pJFF224-NX	RSF1010 replicon, Cm^r T_4 gene 32 promoter, pBluescriptII SK$^-$ polylinker	19
pJFF224-XN	Same as pJFF224-NS except polylinker is in reverse orientation	19
pJFF801	pJFF224-XN::*apxIBD*	This work
pJFF800	pJFF224-NX::*apxICABD*	This work
pJFF750	pBluescript KS$^+$::*apxICABD*	13

In Table 3 of Reimer et al (at page 203 thereof) data on the virulence of said strains in pigs, which were challenged with said strains is shown:

Table 3 Virulence of recombinant and parent *A. pleuropneumoniae* strains in pigs

Challenge Strain[a]	Mortality	Mean lung lesion score	Virulence index[b]
mIT4-H	0/5	1.00	1.00
J45	4/7	3.57	5.60
mIT4-H/pJFF800	7/10	3.10	5.27
mIT4-H/pJFF801	4/9	3.25	4.68

[a]Pigs challenged with J45 and mIT4-H/pJFF800 received 5×10^7 to 1×10^8 CFU. Pigs challenged with mIT4-H/pJFF801 and mIT4-H received 1×10^8 to 5×10^8 CFU.
[b]Virulence index was derived by the equation: VI = (1+mortality ratio) × Mean lung lesion score.

According to the information disclosed in Tables 1 and 3 above, and from the results described in Reimer et al, the strains of *Actinobacillus pleuropneumoniae* described in Reimer et al have the following features:

- Strain J45 is a field isolate, which synthetizes and secretes exotoxins ApxI and ApxII, and it has strong haemolytic and cytolytic activity. It is an immunogenic strain, but virulent.
- Strain mIT4-H is a mutant isolated from J45 following chemical mutagenesis. Its operon apxICABD is completely deleted. This operon is responsible for the synthesis, activation and secretion of exotoxin ApxI, and for the secretion of exotoxin ApxII. Said mutant does not synthetize nor export exotoxin ApxI, but it synthetizes exotoxin ApxII, although it does not export it. It is a non-immunogenic and avirulent strain, which is incapable of protecting pigs

against subsequent challenge with the virulent parent strain J45.

- Strain mIT4-H/pJFF801 is derived from strain mIT4-H, which contains additionally plasmid pJFF801. This plasmid restored only the gene responsible for the excretion of apxIBD. This strain can synthetize and excrete exotoxin ApxII, but not exotoxin ApxI. ApxII is mainly responsible for the haemolytic activity of *Actinobacillus pleuropneumoniae*. Thus, it is a non-immunogenic and virulent strain.
- Strain mIT4-H/pJFF800 is derived from strain mIT4-H, which contains additionally plasmid pJFF800. This plasmid restored operon apxICABD, and the strain can synthetize and secrete exotoxins ApxI and ApxII. The extracelular haemolytic activity is equal or higher than the virulent parent strain J45. Thus, it is an immunogenic and virulent strain.

Hence, none of the strains disclosed in Reimer et al anticipates the immunogenic and non-haemolytic (avirulent) strain subject matter of the present claims, because:

- strains J45 and miT4-H/pjFF800 have the entire relevant genetic information and they are virulent strains,
- strain mIT4-H is a non-immunogenic and avirulent chemical mutant, and
- strain mIT4-H/pJFF801 has genetic modifications and it is virulent and non-immunogenic.

Reimer et al does not teach or suggest that at least one modification in one regime of the *apxIA* gene, and optionally in a segment of the apxIIA gene, which encode a transmembrane domain of the haemolytic and cytolytic Apx exotoxins, would produce an immunogenic and non-haemolytic strain of *Actinobacillus pleuropneumoniae*, as claimed.

The Examiner is further requested to note that strain CECT 5985 and strain CECT 5994 are examples of the immunogenic and non-haemolytic *Actinobacillus pleoropneumoniae* APP strains within the scope of the invention of Group I, and thus should be included within the elected group.

On page 3 of the Office Action, the Examiner issues an further restriction (election of species requirement) as follows:

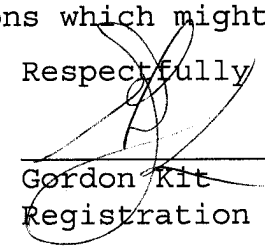
(a) if Group I is elected, one of the species of genes from Claims 16 or 18;

(b) if Group IV is elected, one of the species of genes from Claims 27 or 29.

Applicants respectfully submit that the Examiner's election of species requirement is improper as Claim 1 (Group I) and Claim 24 (Group IV) require a deletion in the *apxIA* (Claims 16 and 27), i.e., the additional election in the *apxIIA* is optional (Claims 18 and 27). Thus, Applicants elect Claims 16 and 27 with traverse on this basis.

The Examiner is invited to contact the undersigned at the below listed number on any questions which might arise.

Respectfully submitted,



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